Title: Trait anxiety, but not state anxiety during critical illness was associated with anxiety and depression over six months after ICU

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Abstract

Objective: To determine the association between anxiety during critical illness and symptoms of anxiety and depression over six months after ICU discharge in survivors of intensive care treatment.

Design: Longitudinal study.

Setting: One closed mixed ICU in an adult tertiary hospital in Brisbane, Australia.

Patients: Participants (n=141) were adults (≥18 years), admitted to ICU for ≥24 hours, able to communicate either verbally or non-verbally, understand English, and open their eyes spontaneously or in response to voice.

Interventions: None.

Measurements and Main Results: The outcomes of symptoms of anxiety and depression over six months after ICU discharge were assessed using the Hospital Anxiety Depression Scale. The primary variable of interest was anxiety during critical illness. Two components of anxiety (state and trait) were assessed during critical illness using the Faces Anxiety Scale and the trait component of the State-Trait Anxiety Inventory. Perceived social support, cognitive functioning and post-traumatic stress symptoms were also assessed using standardised instruments. Clinical and demographic data were obtained from patients and medical records. Participants were followed-up in hospital wards, and at three and six months after ICU discharge.

During ICU treatment, 81 (57%) of the 141 participants reported moderate to severe levels of state anxiety. Of the 92 participants who completed the surveys at the six-month follow-up, 26 (28%) reported symptoms of anxiety and 21 (23%) symptoms of depression. Symptoms of anxiety and depression were strongly

correlated in this cohort of survivors. Trait anxiety was significantly associated with both anxiety and depression symptoms over time, however, state anxiety was not associated with either outcome. Participants who reported post-ICU memories of intra-ICU anxiety were significantly more anxious during recovery over six months. Cognitive functioning and post-traumatic stress symptoms were both significantly associated with anxiety and depression symptoms over time.

Conclusion: Symptoms of anxiety and depression are a significant issue for general ICU survivors. Trait anxiety was significantly associated with adverse emotional outcomes over six months after ICU discharge. There was also a significant relationship between post-ICU memories of intra-ICU anxiety and anxiety during recovery. Interventions to reduce anxiety during critical illness need to be considered and evaluated for their longer term benefits for survivors of critical illness.

Introduction

Survival from critical illness has improved significantly over the years with most patients discharged alive from hospital. For some survivors however, the recovery process can be physically and emotionally challenging. Numerous observational studies have reported on the emotional problems, including symptoms of anxiety and depression, that patients experience after critical illness. The prevalence of these emotional problems in intensive care unit (ICU) survivors is relatively high with around a third of patients reporting adverse emotional outcomes (1-5).

The widespread nature of this problem has led researchers to explore factors associated with adverse emotional outcomes (6, 7). Anxiety during critical illness has repeatedly been suggested as important (6, 8, 9). Anxiety is a complex phenomenon that comprises of two components: state and trait (10, 11). State anxiety is defined as a normal and temporary emotion that involves physiological arousal and feelings of tension, apprehension, nervousness and worry when a stressful situation is perceived. Trait anxiety, on the other hand, corresponds to a person's tendency to become state anxious as part of their personality trait (10, 11). To achieve a comprehensive understanding of anxiety during critical illness in our cohort of survivors, both components of anxiety (state and trait) were explored. We hypothesised that state and trait anxiety would be associated with anxiety and depression symptoms over time after ICU discharge.

The aim of this study was to determine the association between anxiety during critical illness (state and trait) and symptoms of anxiety and depression in survivors of critical illness over six months post ICU discharge.

Materials and Methods

This longitudinal cohort study of general ICU survivors was conducted in one closed mixed medical/surgical/trauma ICU of a tertiary metropolitan public hospital located in Brisbane, Australia. The Intensive Care Unit has 25 beds and provides 24 hours intensivist led care with a registered nurse-patient ratio of 1:1. During the time of enrolment (September 2012–February 2013) there were approximately 1,100 admissions to this ICU. The Princess Alexandra Hospital (HREC/12/QPAH/173) and Griffith University (NRS/35/12/HREC) Ethics Committees approved this research. All participants provided written informed consent. The study protocol has previously been published (12). However, a summary of the methods and modifications made to the published protocol are provided in this section.

Patients

Participants were adults (≥18 years), admitted to the ICU for ≥24 hours, able to communicate either verbally or non-verbally (pointing, gestures, written, mouthing, etc.), understand English, and open their eyes spontaneously or in response to voice (visually intact or sufficient corrected vision).

Data Collection

Study participants provided information in ICU, in the hospital wards, and at three and six months post ICU discharge. Participants were followed-up in the hospital wards (within three weeks of ICU discharge) to confirm their wish to participate in this study, obtain written informed consent and complete the first set of self-reported questionnaires (Table 1). At three and six-month follow-up participants were contacted by a phone call to remind them about their involvement in this study before posting the

surveys. An appointment for a phone interview was scheduled for those participants who wished to provide the answers to the researcher over the phone. Most participants returned the surveys in the reply paid envelope provided, twelve participants read their answers to the researcher over the phone, and two participants preferred to use email.

State anxiety was assessed twice a day (morning 8-11am and afternoon 4-7pm) up to 30 days during ICU stay. These timeframes were selected to identify any difference between morning assessments (usually busier ICU environment) and evening assessments (usually quieter ICU environment). Patient's competency to report on their level of state anxiety was determined by consultation with the bedside registered nurse and patient's ability to communicate effectively (verbally or not verbally) with the researchers.

The assessment of trait anxiety was performed once only when participants were in the wards for two reasons: [1] The State-Trait Anxiety Inventory (STAI) Form Y-2 is a 20-Item instrument, with completion requiring a patient to be able to maintain attention for about 10 minutes. [2] Trait personalities are stable patterns of cognition, affective reactions and behavior that are relatively consistent across time and situations (13). Thus, trait anxiety would have been unlikely to change in such a short period (between ICU stay and assessment in the wards). The principal investigator and the ICU Research Nurse conducted the state anxiety assessments in ICU and assisted the participants (when needed due to physical impairment) with the surveys in hospital wards.

Clinical and demographic data collected from medical records included: age, gender, type of admission (medical, surgical, trauma, cardiac surgery), delirium (Confusion Assessment Method – ICU: CAM-ICU), hours of mechanical ventilation

(invasive and non-invasive), acute physiology and chronic health evaluation III score (APACHE III), length of ICU stay (days), length of hospital stay (days) and pain using the Critical-Care Pain Observation Tool (CPOT) (14-17). Data on drugs administered included exposure to corticosteroids, opioids, benzodiazepines, anxiolytics, antidepressants, beta-blockers, anesthetic agents and analgesics; length of sedation and analgesia (hours of propofol, midazolam, morphine, fentanyl, ketamine, oxycodone infusion); and total doses of sedatives and analgesics (propofol, midazolam, morphine, fentanyl, ketamine, oxycodone and paracetamol).

Data collected in the hospital wards using a questionnaire included: marital status, employment status and level of education, pre-ICU medications (benzodiazepines, anxiolytics, antidepressants, corticoids, opioids, and beta-blockers), smoking status and evidence of mental health treatment. Participants who answered "Yes" to either of the following two question was considered to have evidence of mental health treatment prior to the ICU admission: [1] Have you ever visited a general practitioner or a mental health professional for symptoms of psychological distress or emotional problems? [2] Were you taking benzodiazepines, anxiolytics or antidepressants medications within the 12 months prior to the ICU admission? Mental health history was assessed using this approach to capture any indication of mental health problems prior to the ICU admission more thoroughly than was likely if relying on mental health history from medical records. A similar approach has previously been used in a cohort of ICU patients (18). The demographic questionnaire is provided as Supplementary Material 1.

Instruments used in this study are outlined in Table 1 and included: the Post-traumatic Stress Symptoms 10-Question Inventory (PTSS-10), trait component of the

State-Trait Anxiety Inventory (STAI) for Adults Form Y-2, Hospital Anxiety and Depression Scale (HADS), Faces Anxiety Scale (FAS), Multidimensional Scale of Perceived Social Support (MSPSS), Life Orientation Test-Revised (LOT-R) and Cognitive Functioning Scale Medical Outcome Study 6-Item (MOS COG). These tools were chosen because they are self-reported, well validated and easy to understand instruments, take a few minutes to complete, and with the exception of Cognitive Functioning Scale Medical Outcome Study 6-Item (MOS COG), have all been used in ICU research (11, 19-24).

Information about pre-ICU medications, social support, cognitive functioning, trait optimism and post-traumatic stress symptom (PTSS) were collected because the literature suggests a possible association between these factors and adverse emotional outcomes after ICU (25-28).

Data analysis

Power analysis *a priori* using G*Power was performed to estimate the sample size of this study (29). Multiple regression test (fixed model, R^2 increase) with a power of 80%, a significance level of α=0.05 and a medium size effect (0.15) were selected. The effect size was estimated from previous research exploring similar research questions (30, 31). In addition, we expected a maximum of seven variables to be included in the final model, a mortality rate of 10% and a dropout of 30% at six months. Thus, it was estimated that we needed 104 participants at six months follow up.

Stata version 13 (Statacorp, College Station, Texas) was used for all analysis (32). Data were cleaned and checked for missing, invalid and outlying values. A random selection (15%) of the database was verified against original questionnaires. Categorical

data were reported as percentages and continuous data as means and standard deviations (SDs) or medians and interquartile ranges (IQRs). Comparisons of the characteristics of responders and non-responders were made using Chi-square or Fisher's exact test, t-test for differences in means, and nonparametric tests for rank differences.

The independent variable "state anxiety" was derived from repeated measures taken during the participants ICU stay (twice a day up to 30 days). The first state anxiety measure in ICU and several aggregate variables were extensively explored to obtain a single value that best represented the level of state anxiety during the patient's ICU stay. Of all derived (aggregated) measures for anxiety, the mean value was the strongest at accounting for correlations amongst observations in the same cluster. Participants were categorised as low anxious (state anxiety mean score 1-2) and moderate to severe anxious (state anxiety mean score 3-5) (21).

Variables associated with the outcome ($p<0.20$) on bivariate analysis were selected for models. Selected variables were checked against one another for multicollinearity using Spearman correlations and Chi-square. After this process, variables were ranked from most to the least significant and entered into the model. Mixed effect regression models with a random intercept per subject were used to assess the independent association of each factor with symptoms of anxiety and depression while accounting for repeated data from the same participants. Mixed model analysis is used in longitudinal studies to adjust for dependency of repeated observations (account for correlated observations within one subject over time). Time is explicit with observations over time nested within subject (33). In other words, all data from measures obtained serially such as cognitive functioning, PTSS and social support were included in the mixed model analysis and adjusted for dependency over time. Mixed

models also better handle missing data by using available data from all subjects regardless of whether their data are complete.

The Akaike Information Criteria (AIC) along with statistical significance ($p<0.05$) were used to identify the best set of variables significantly and independently associated with adverse emotional outcomes (symptoms of anxiety and depression). Theory-grounded factors were added into the 'final set' of variables to check whether they influenced the model (i.e. were significant and/or decreased/improved the AIC). Potential interaction effects were assessed using the likelihood ratio test (LR), comparing the final anxiety and depression models (with no interaction term) against models with one interaction term at a time. The importance of interaction effects were based on the results of LR test, where $P>0.05$ indicated a non-significant interaction. The potential impact of missing data was investigated using a descriptive approach, comparing the baseline data of responders and non-responders from subsequent follow-up points.

Model results are expressed as unstandardized coefficients, 95% confidence intervals and *p*-values. Model diagnostics included assessment of influential observations, multicollinearity amongst variables and residual checks.

Results

In total 797 patients were screened with 141 enrolled between September 2012 and February 2013. From 141 participants enrolled, 120 consented to participate in the follow-up. One hundred and one (84%) participants completed three-month follow-up and 92 (77%) completed six-month follow-up (Figure 1). Participants were a mixed medical (49%), surgical (34%) and trauma (17%) group of ICU patients with an average age of 54 (standard deviation, SD±15) years, and 70% were male. The median length of

ICU stay and hospital stay were 4 [interquartile range, IQR: 3-7] days and 15 [10-28] days, respectively. The majority of participants required invasive mechanical ventilation (82%) for about 52 [13-148] hours, and the median APACHE III score of this sample was 58 [43-74].

Symptoms of anxiety (HADS≥8) were reported by 42% of the participants while in the hospital wards, 26% at three-month and 28% at six-month follow-up. Symptoms of depression (HADS≥8) were reported by 37% of the participants while in hospital wards, 19% at three-month and 23% at six-month follow-up. Symptoms of anxiety decreased significantly from hospital to assessment at three-month after ICU discharge (7.0 [4.0-10.0] vs. 5.0 [2.5–8.0], $p<0.001$). Symptoms of depression also decreased significantly over the same period (5.5 [3.0–9.0] vs. 3.0 [2.0 – 6.0], $p<0.001$). No significant change was observed from three to six-month follow-up on either symptoms of anxiety or depression. Participants moved between categories (symptomatic/asymptomatic) of anxiety and depression over time. Some participants who scored within normal limits (HADS<8) in the wards presented with symptoms of emotional distress at three and or six months and vice versa (Figures 2 and 3).

Most participants (82%) reported state anxiety in ICU, with 57% reporting moderate to severe levels (FAS 3-5). When considering the 604 individual anxiety assessments, participants reported some level of anxiety 393 (65%) of the time, with 173 (44%) of these being moderate to severe levels. While the levels of state anxiety fluctuated over time, there was no significant difference between morning and afternoon assessments.

The levels of trait anxiety in the study participants were very similar to the Australian population (36.0 [29.0-47.0]) (34). The mean trait optimism (14.7, SD±4.2)

was also similar to population-base norms and another cohort of ICU patients (5, 35). Delirium was present in 11 (8%) participants and pain in 65 (46%) participants. The most common sedatives and analgesics administered were propofol (84%), fentanyl (79%), midazolam (35%) and morphine (26%). Other demographic information and data about medications administered during ICU treatment are presented in Table 2.

Perceived levels of social support did not change from three months to six months post ICU discharge (6.0 [5.3-6.6] vs. 6.0 [5.0-6.5] p=0.088) and they were similar to the ones reported in other populations (22). On the contrary, perceived cognitive functioning increased significantly from hospital to assessment at three months after ICU discharge (56.7 [40.8-70.0] vs. 63.0 [57.0-77.0] p<0.001). No significant increase was observed from three to six months. Despite the initial increase in perceived cognitive functioning, these levels are well below population-based norms (24). Approximately 58-76% of participants reported traumatic memories of their ICU admission at each of the follow-up points. Changes in the proportion of participants who presented with traumatic memories of the ICU admission across the three-time points measured (in the wards, three and six months after ICU discharge) are presented in Supplementary Material 2. The prevalence of PTSS was similar at three and six months (n=19, 19% vs. n=15, 17%).

Participants who completed six-month follow-up were similar to non-responders in gender, length of ICU stay, length of hospital stay and APACHE III score. Non-responders were younger and reported higher levels of anxiety (state and trait) in hospital than the responders (Table 3). These differences were similar at three and six-month follow-up.

Linear mixed effect models showed a decline in anxiety symptoms over six months after ICU discharge. The most significant drop occurred from ICU to three months (β=-0.8, 95% CI -1.5, -0.1, $p<0.02$). Trait anxiety, symptoms of depression during recovery, self-reported cognitive functioning, memories of anxiety in ICU, evidence of mental health treatment prior to the ICU admission and six month PTSS score were all significantly associated with symptoms of anxiety over six months after ICU discharge (Table 4). Symptoms of depression decreased over the six months after ICU discharge. Symptoms of anxiety during recovery, trait anxiety, self-reported cognitive functioning and reason for ICU admission (trauma patients) were all significantly associated with symptoms of depression over the six months after ICU discharge (Table 5).

The likelihood- ratio test established no significant interaction effects in the final anxiety and depression models. Descriptive analyses of missing data showed non-responders at three months follow-up reported higher baseline anxiety and depression scores than responders. These differences were no longer significant at six months. Non-responders at three and six months reported higher trait anxiety levels, more evidence of mental health treatment prior to ICU admission and more post-ICU memories of anxiety than responders at the baseline.

Discussion

In this study, we identified factors associated with symptoms of anxiety and depression over six months after intensive care treatment in survivors of critical illness. The role of anxiety during critical illness on adverse emotional outcomes during recovery was the primary focus of this study.

Symptoms of anxiety and depression decreased significantly from the period in hospital to three months after discharge with no further significant change from three to six months after ICU discharge. These findings are in line with those reported recently in a nonsurgical cohort of critically ill patients (36). Anxiety and depression symptoms were present in around a quarter of our study participants at six months, numbers that were similar to those found in other studies (3, 4, 6, 31, 37). Some participants in this cohort moved between asymptomatic and symptomatic categories over time. These changes showed that symptoms of emotional distress had a delayed onset in some participants, resolved rapidly in others and appeared at varied stages during recovery. Ongoing health issues may be one potential explanation for the delayed onset of these symptoms.

The majority of participants reported some degree of state anxiety while in ICU with over half of these reporting moderate to severe levels. These findings are in line with the current understanding of state anxiety in ICU and highlight the need to improve the assessment and management of this symptom in the ICU setting (21).

Mixed effect regression models revealed that common factors associated with symptoms of both anxiety and depression over six months after ICU discharge in our sample were trait anxiety, cognitive impairment and PTSS. Trait anxiety showed a clear association with symptoms of anxiety and depression; to our knowledge no previous study has reported this association. Impaired cognition has previously been associated with anxiety and depression symptoms in critical illness survivors (38-41).

PTSS were associated with both anxiety and depression, however these associations appeared to be significant at varying time points. PTSS at three months were associated with depression and PTSS at six months with anxiety. These variations

also suggest that interventions need to be tailored to individual patients because their need for support is likely to change over time.

Symptoms of depression and anxiety were correlated with each other. While no study testing this relationship in the ICU population was located, anxiety and depression disorders are often comorbid with each other (42, 43). A recent large multicentre cohort study found the majority of the critical care participants who experienced PTSS also had depression symptoms (44). It is not surprising in our study therefore to have found a relationship between symptoms of anxiety and depression and post-traumatic stress.

Factors associated exclusively with anxiety symptoms over time were post-ICU memories of anxiety during ICU treatment and evidence of mental health treatment prior to ICU admission. Only the recall of extremely stressful ICU experiences had previously been identified as a factor for anxiety symptoms during recovery (45). Patients with mental health history are commonly excluded from studies in this field to reduce bias when assessing emotional outcomes after ICU discharge. In this study, we chose to include participants who had evidence of mental health treatment prior to the ICU admission and in this cohort this history appears to be an important risk factor. Collecting information about mental health treatment (history and medications) prior to ICU allowed us to identify a negative association between symptoms of anxiety and previous mental health treatment. The continuation of usual treatment received by these participants might have reduced the burden of anxiety symptoms after the intensive care experience but we did not specifically measure ongoing treatment (6, 46). Evidence of mental health treatment was not significantly associated with symptoms of depression in the multivariate analysis. The meaning of this lack of association is unclear.

The only factor associated exclusively with depression symptoms was ICU

admission due to trauma. With the design used in this study, it is not possible to distinguish between the effects of the initial trauma and the effects of the health care such as ICU treatment on depression during recovery.

As mentioned previously, only the trait component of anxiety was associated with symptoms of anxiety and depression during recovery, the state component was not associated with either outcome. While there was a moderate correlation between state and trait anxiety, state anxiety did not appear to have any long-term effect on adverse emotional outcomes. This finding was unexpected since we had thought that state anxiety was a hidden factor for symptoms of anxiety and depression after ICU. This rationale was based on the fact that sedation is often regarded as a predictor of adverse emotional outcomes, but with unclear mechanisms for this association. This uncertainty raised the idea that high levels of state anxiety in ICU might have been a key factor in this relationship (6, 8, 9). Although state anxiety was not a significant factor for anxiety and depression symptoms, the recall of being anxious in ICU was significantly associated with anxiety symptoms over six months after discharge in our participants (45).

A number of studies in this area have incorporated follow-up of patients at varying time points during recovery. However some of these studies have not sufficiently adjusted for dependency of observations over time in their analyses or used techniques that deal with missing values such as mixed model analysis. This has potentially led to results not fully capturing the dynamic nature of the recovery process of these patients. In the present study we adopted statistical techniques that model the sources of variation and correlation that arise in longitudinal data sets with multiple missing data points. Mixed model analysis deals with missing values in such a way that

missing scores have no effect on other scores from the same patient. In addition, it includes all data available, not only those cases with complete information.

Potential limitations of this study need to be noted. In this longitudinal study, we identified factors associated with symptoms of anxiety and depression, but this study was not designed to test any causal relationships. In addition, although we assessed symptomatology of adverse emotional outcomes using validated tools, clinical diagnoses of anxiety, depression and post-traumatic stress were not made. While we measured numerous factors previously identified in the literature, it is possible that factors other than those measured here may have influenced the outcomes. The sample size was small, however it represented the Australian ICU population well and was comparable to other studies in this area (1, 6, 21). Although follow-up rates at three and six months were good, the trend for participants lost to follow-up to be younger and more likely to suffer from higher anxiety levels (state and trait) may have resulted in bias. Participants self-reported cognitive functioning by using the MOS 6-Item Cognitive Functioning Scale, this instrument needs further validation in ICU survivors. Although traumatic memories of anxiety were significantly associated with anxiety symptoms over time, these memories might have been biased by ongoing or current anxiety. While trait anxiety was assessed in hospital, trait anxiety may not represent a factor associated with critical illness, but participant's individual personality characteristics. It is worth noting that the levels of trait anxiety found in this sample were similar to the general Australian population suggesting that critical illness survivors with high anxiety personality trait may be at greater risk of developing anxiety and depression. Evident descriptive differences in responders and non-responders in terms of trait anxiety levels, evidence of mental health treatment prior to ICU admission

and post-ICU memories of anxiety could potentially influence model estimates by underestimating or overestimating the effect sizes. Further, multiple imputations to assess the possibility that the produced estimates might be biased due to missingness were not performed.

This study adds to the body of research assessing long-term recovery from critical illness, specifically factors related to emotional problems such as anxiety and depression in ICU survivors. Incorporation of these findings into the development and implementation of relevant interventions in acute and post-acute settings has the potential to reduce adverse emotional outcomes in ICU survivors. This research adds to the current literature identifying anxiety and depression symptoms as an important problem for survivors of critical illness and that early detection of these symptoms might be beneficial for long-term recovery.

Conclusions

Findings of this research highlight the ongoing adverse emotional outcomes in survivors of critical illness as well as the need for the development and implementation of strategies to reduce these symptoms. Because of the long-term effects of critical illness and the delayed onset of symptoms in some patients, not only should these interventions take place during intensive care treatment but also at different time points after ICU discharge. Interventions to address anxiety during critical illness should be directed to target both the state and trait components.

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Figure Legends

Figure 1. Longitudinal cohort study of general ICU survivors. Study flow chart

Figure 2. Anxiety scores of survivors of critical illness over the 6 months following ICU discharge

Figure 3. Depression scores of survivors of critical illness over the 6 months following ICU discharge

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Supplementary materials

Supplementary material 1. Patient demographics questionnaire

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Tables and figures

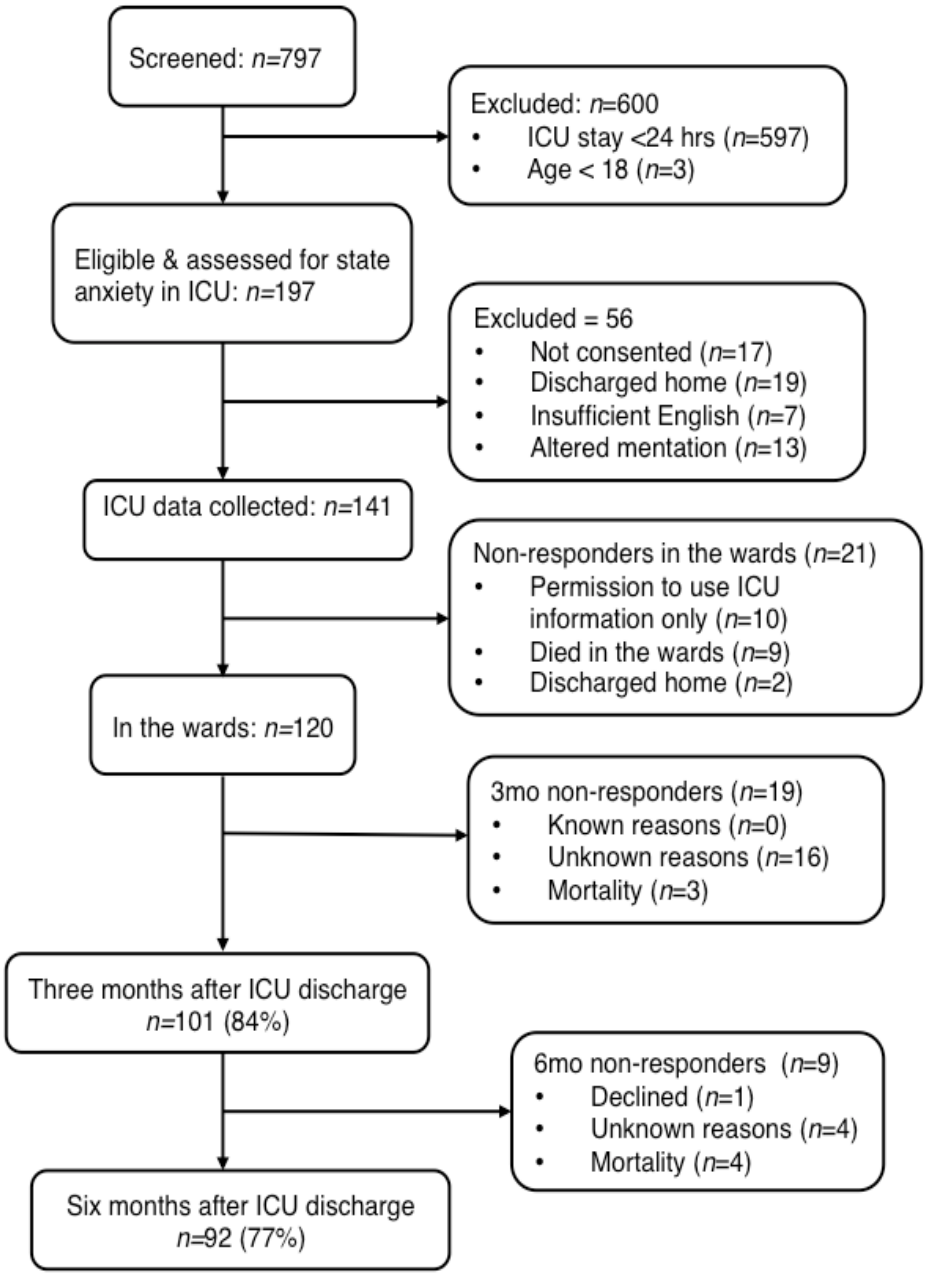


Figure 1. Longitudinal cohort study of general ICU survivors. Study flow chart

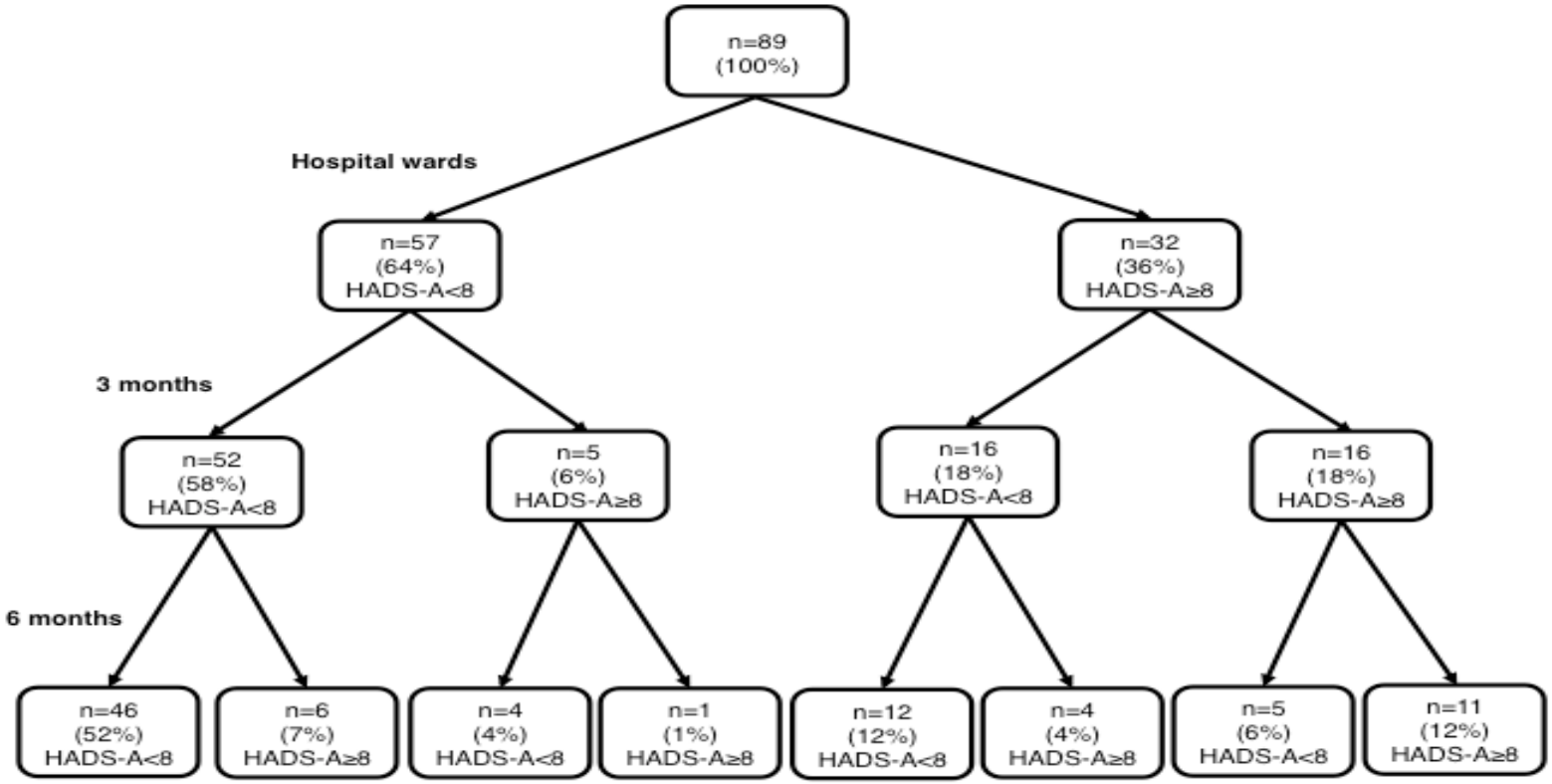


Figure 2. Anxiety scores of survivors of critical illness over the 6 months following ICU discharge

Participants who reported on the Hospital Anxiety and Depression Scale-Anxiety Subscale (HADS-A) at all time points were included in this diagram (n=89). Participants with missing data on the HADS-A at any time point measurement (n=31) were not included. HADS-A score<8 = asymptomatic, HADS-A score ≥8 = symptomatic.

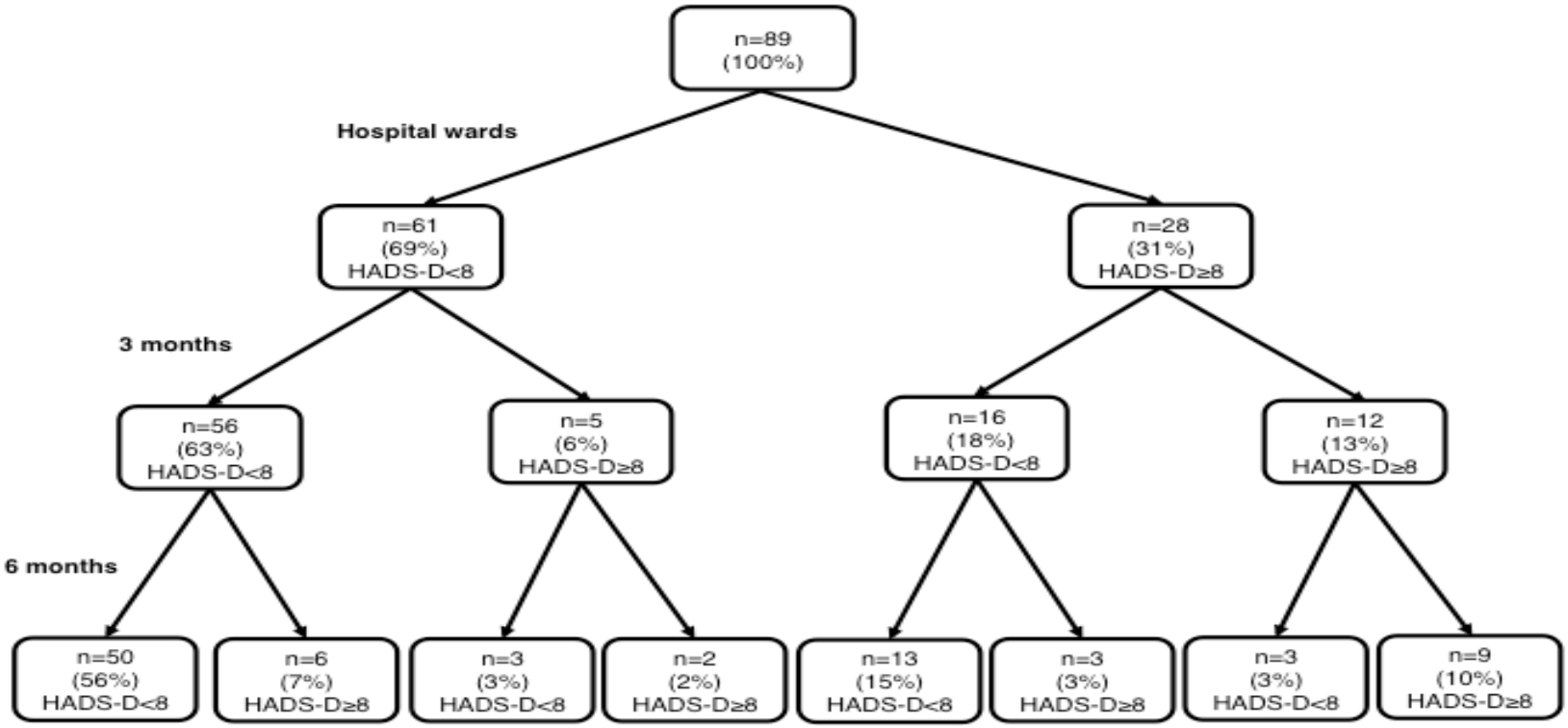


Figure 3. Depression scores of survivors of critical illness over the 6 months following ICU discharge

Participants who reported on the Hospital Anxiety and Depression Scale-Depression Subscale (HADS-D) at all time points were included in this diagram (n=89). Participants with missing data on the HADS-D at any time point measurement (n=31) were not included. HADS-D score<8 = asymptomatic, HADS-D score ≥8 = symptomatic.

Table 1. Study constructs, instruments and data collection schedule

Construct	Instrument	Number of items	Possible score	Measurement time points	Comments
State anxiety	Faces Anxiety Scale (FAS)	1	1-5	In ICU Twice a day (morning 8-11 and afternoon 4-7)	Each of the five faces of this tool represents a different level of anxiety ranging from no anxiety (1) to extreme anxiety (5). Patients were shown the FAS and asked to rate their levels of anxiety by indicating the face that better represented how much anxiety they felt at the moment of assessment.
Trait anxiety	Trait component of the State-Trait Anxiety Inventory (STAI) for Adults Form Y-2	20	For each item, a rating score between 1 and 4 is possible. Total score 20-80	Hospital wards within three weeks after ICU discharge	Higher scores indicate greater levels of trait anxiety.
Trait Optimism	Life Orientation Test-Revised (LOT-R)	10	For each item, a rating score between 0 and 4 is possible. Total score 0-24	Hospital wards within three weeks after ICU discharge	6 items concerning general expectations relative to positive or negative consequences. 4 filler items not used in the scoring. Higher scores indicate greater optimism.
Symptoms of anxiety and depression	Hospital Anxiety and Depression Scale (HADS)	This tool has two subscales Depression: 7 items Anxiety: 7 items Total: 14 items	For each item, a rating score between 0 and 3 is possible. Total score for each subscale 0-21	Hospital wards within three weeks after ICU discharge and at three and six-month follow-ups	The total score for each subscale can be classified into four categories: normal (0-7), mild (8-10), moderate (11-14) and severe (15-21).
Social support	Multidimensional Scale of Perceived Social Support (MSPSS)	12	For each item a rating score between 1 (very strongly disagree) and 7 (very strongly agree) is possible. Total score 12-84	Three and six-month follow-ups	Three subscales: family, friends and significant other. Higher scores indicated higher levels of perceived social support.
Self-perceived cognitive	Cognitive Functioning Scale	6	Each item is scored from 1 (all the time) to 6	Hospital wards within three weeks after ICU	Self-reported cognitive functioning. This tool contains questions assessing areas of memory,

functioning	Medical Outcome Study 6-Item (MOS COG)		(none of the time). Summing the individual item scores and transforming the resulting score to a 0-100 scale calculate the total score.	discharge and at three and six-month follow-ups	attention and reasoning. Higher scores indicate better cognitive functioning.
Posttraumatic Stress Symptoms and traumatic memories of the ICU experience	Posttraumatic Stress Symptoms 10-Question Inventory (PTSS-10)	This tool has two parts Part A: 4 memories Part B: 10 symptoms	Part A: for each memory, a Yes (presence of memory) or No (absence of memory) answer can be selected. Part B: for each symptom, a rating score between 1 (never) and 7 (always) were possible. Total score 10 to 70	Part A: Hospital wards within three weeks after ICU discharge and at three and six-month follow-ups Part B: Three and six-month follow-ups	This questionnaire has two-parts (part A and B). Part A consists of four traumatic memories of their ICU stay (memories of nightmares, severe anxiety or panic; severe pain; and feelings of suffocation). In part B, the presence and intensity of 10 posttraumatic symptoms are assessed. Total score can be classified into two categories: high probability of PTSD (total score ≥ 35 points) and low probability of PTSD (< 35 points).

FAS = Faces Anxiety Scale, PTSD = Posttraumatic Stress Disorder

Table 2. Demographic and clinical characteristics

Variable	Frequency (%) n=120
Marital status	
Married/De facto	73 (61)
Never married	24 (20)
Separated/Divorced	19 (16)
Widowed	4 (3)
Level of education	
Primary/secondary school (years 8-10)	47 (39)
Secondary school (years 11,12)	26 (22)
Trade/vocational/Diploma	26 (22)
University	21(17)
Employment status	
Full time work	49 (41)
Part time/casual	19 (16)
Retired	25 (21)
Student/other	4 (3)
Disability benefit	18 (15)
Unemployed	5 (4)
Smoking status	
Yes	33 (28)
No	87 (72)
Evidence of mental health treatment	
Yes	45 (37)
No	75 (63)
Corticoids (prior to ICU admission)	
Yes	15 (12)
No	105 (88)
Opioids (prior to ICU admission)	
Yes	16 (13)
No	104 (87)
Benzodiazepines/antidepressants/anxiolytics (prior to ICU admission)	
Yes	24 (20)
No	96 (80)
Beta-blockers (prior to ICU admission)	
Yes	25 (21)
No	95 (79)

Variable	Median (IQR) n=141
Length of sedation and analgesia (hours)	
Propofol (n=116)	23 (7-83)
Fentanyl (n=80)	46 (15-94)
Midazolam (n=47)	36 15-109)
Morphine (n=26)	30 (15-85)
Ketamine (n=8)	40 (9-80)
Total doses of sedatives, analgesics and corticoids (milligrams)	
Propofol (n=119)	2960 (750-11290)
Fentanyl (n=111)	4 (1-7)
Midazolam (n=49)	101 (17-218)
Morphine (n=37)	48 (9-161)
Ketamine (n=8)	260 (36-350)
Hydrocortisone (n=10)	450 (325-588)
Oxycodone (n=38)	10 (5-65)
Paracetamol (n=120)	7500 (4000-14750)

Table 3. Comparison between responders and non-responders at six months follow up (n=141)

	Responders n=92	Non-responders n=49	*p*-value
	Mean (SD)		
Age[a]	56.8 (13.5)	49.0 (17.3)	0.008[c]
	Median (IQR)		
APACHE III score[a,b]	56.0 (41.5-72.7)	62.0 (44.5-75.0)	0.569
Length of ICU stay (days)[a]	4.0 (3.0-7.0)	5.0 (2.5-11.0)	0.219
Length of Hospital stay (days)[a]	14.5 (9.3-25.8)	17.0 (9.2-29.0)	0.456
FAS State Anxiety in ICU[a,b]	2.0 (1.2-3.0)	3.0 (1.7-3.5)	0.029[c]
STAI Form –Y Trait anxiety[b,d]	35.0 (28.0-42.0)[e]	45.5 (34.5-51.5)[e]	0.001[c]
	Frequency (%)		
Gender[a]			
Male	66 (72)	32 (65)	0.550
Female	26 (28)	17 (35)	

[a] Calculated from baseline (ICU) data
[b] APACHE: Acute Physiology and Chronic Health Evaluation System; STAI: State and Trait Anxiety Inventory; FAS: Faces Anxiety Scale; HADS: Hospital Anxiety Depression Scale
[c] Significant ≤0.05
[d] Calculated from assessment in the hospital wards (n=121)
[e] Responders=90 Non-responders=31
T-test for normally distributed (age), Mann-Whitney test for not normally distributed (APACHE III score, length of ICU stay, Length of hospital stay, state anxiety in ICU, HADS-Anxiety and HADS-Depression) and Chi-Square test for categorical variables (gender).

Table 4. Linear Mixed Model: factors associated with symptoms of anxiety over six months after ICU discharge (n=120)

Factors	**Coefficient (95% CI)**	***p-value***
(Intercept)	2.90 (0.77, 5.01)	0.007
Time 2 (3 months)	-0.83 (-1.49, -0.16)	0.015
Time 3 (6 months)	-0.55 (-1.21, 0.10)	0.100
Cognitive functioning (per 10 units) (score range 0-100)	-0.41 (-0.64, -0.19)	<0.0001
Symptoms of depression (per unit) (score range 0-21)	0.37 (0.27, 0.48)	<0.0001
Trait anxiety (per 10 units) (score range 20-80)	0.63 (0.20, 1.06)	0.004
Post-traumatic stress symptoms at 6mo (per 10 units) (score range 10-70)	0.63 (0.30, 0.97)	<0.0001
Memories of experiencing anxiety during ICU stay		
No	Reference	
Yes	0.84 (0.17, 1.51)	0.014
Evidence of treatment for Mental health prior to ICU admission		
No	Reference	
Yes	-0.92 (-1.8, -0.09)	0.029

Akaike Information Criteria (AIC) for base model=1612, n=310; AIC for best model= 1235, n=264

Table 5. Linear Mixed Model: factors associated with symptoms of depression over six months after ICU discharge (n=120)

Factors	**Coefficient (95% CI)**	***p-value***
(Intercept)	1.13 (-1.11, 3.38)	0.323
Time 2 (3 months)	-0.49 (-1.15, 0.16)	0.145
Time 3 (6 months)	-0.30 (-0.99, 0.37)	0.373
Cognitive functioning (per 10 units) (score range 0-100)	-0.46 (-0.68, -0.23)	<0.0001
Symptoms of anxiety (per unit) (score range 0-21)	0.43 (0.33, 0.54)	<0.0001
Trait anxiety (per 10 units) (score range 20-80)	0.75 (0.34, 1.15)	<0.001
Post-traumatic stress symptoms at 3mo (per 10 units) (score range 10-70)	0.54 (0.18, 0.89)	0.003
Reason for ICU admission		
Medical	Reference	
Surgical (Incl. cardiac surgery)	-0.39 (-1.21, 0.41)	0.337
Trauma	1.72 (0.58, 2.85)	0.003

Akaike Information Criteria (AIC) for base model=1612, n=310; AIC for best model= 1358, n=264

Supplementary material 1

PATIENT DEMOGRAPHICS QUESTIONNAIRE

Please answer the following questions about yourself by underlying the answer that corresponds to you:

1. **Marital status:**

   Married Never married De facto Separated Divorced Widowed

2. **Highest level of education completed:**

   Primary school
   Secondary school (Grades 8, 9, 10)
   Secondary school (Grades 11, 12)
   Vocational/Apprenticeship/Trade Certificate
   Associate Diploma/Diploma
   Undergraduate Degree
   Postgraduate Degree
   Other (please list) _____

3. **Employment status before the ICU admission:**

   In paid Full time work
   In paid Part time work
   In paid Casual work
   If in paid work, how many hours per week do you usually work? _____
   Retired
   Student
   On Disability Benefit
   Unemployed
   Other (Please specify) _____

4. **Have you ever visited a general practitioner (GP) or a mental health professional for symptoms of psychological distress or emotional problems?**

   Yes No

5. **Please record how often in the last 12 months you have smoked (please underline).**

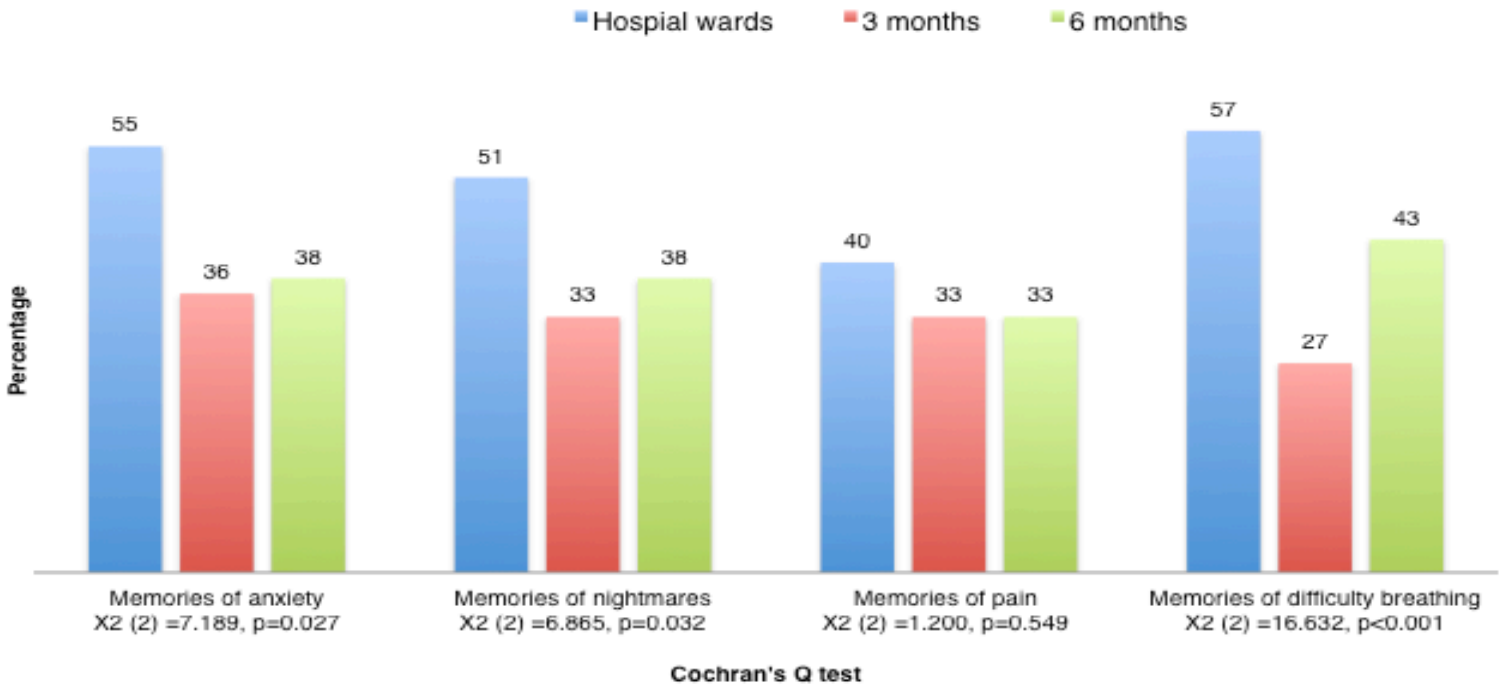
   Daily Weekly Less than weekly Ex-smoker Never-smoker

6. **How many cigarettes (manufactured or roll-your own) did you used to smoke per day previous to the ICU stay?_____**

7. **Where you taking any of the following medications before the ICU admission (12 months?**

Corticosteroids replacement therapy (Hydrocortisone, prednisone, prednisolone) Other, please list _____	Yes	No
Opioids (e.g. morphine, MSContin, OxyContin, fentanyl, methadone, etc.). Other, please list_____	Yes	No
Benzodiazepines, anxiolytics, antidepressant (e.g. diazepam, alprazolam, oxazepam). Other, please list_____	Yes	No
Beta-blockers (e.g. propranolol, metoprolol). Other, please list_____	Yes	No

Supplementary material 2



Supplementary material 2. Changes in the proportion of patients who presented with traumatic memories of the ICU admission across the three-time point measurement. Participants who reported on Part A of the Post-traumatic Stress Symptoms 10-Question Inventory (PTSS-10) at all time points were included in this analysis (n=88). Participants with missing data on the Part A of the PTSS-10 at any time point measurement (n=32) were not included.